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REPORT OF

WORKSHOPS ON EPIDEMIOLOGIC STUDIES OF AIRBORNE PARTICULATES

Research Triangle Park April 3-4, 1980

University of Pittsburgh June 9-10, 1980

by

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16. ABSTRACT

The report represents the cumulative effort of both the members of the Workshop on Epidemiologic Studies of Airborne Particles and EPA staff. The workshop was conducted after EPA developed a Problem Definition Study for Epidemiologic Studies on Airborne Particles. The report presents the recommendations that the workshop members prepared to assist the EPA in developing a research program to ascertain the biomedical effects of inhalable particulate matter. This definition of research was accomplished by identification of gaps in current knowledge, identification of research that needs to be performed to fill these gaps, and determination of research that has a high probability of providing a clear examination of the health effects of particles.

A summary of the recommendations follows:

- To study acute and chronic respiratory and acute cardiovascular diseases, in relation to exposure to airborne particles, a single cross-sectional prospective investigation involving several institutions should be given priority.
- Investigation of stomach cancer in relation to airborne particles is recommended.
- Adequate exposure estimates must be made.
- Quality assurance/control of all measurements is very important.

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FOREWORD

The many benefits of our modern, developing, industrial society are accompanied by certain hazards. Careful assessment of the relative risk of existing and new man-made environmental hazards is necessary for the establishment of sound regulatory policy. These regulations serve to enhance the quality of our environment in order to promote the public health and welfare and the productive capacity of our Nation's population.

The Health Effects Research Laboratory, Research Triangle Park, conducts a coordinated environmental health research program in toxicology, epidemiology, and clinical studies using human volunteer subjects. These studies address problems in air pollution, non-ionizing radiation, environmental carcinogenesis and the toxicology of pesticides as well as other chemical pollutants. The Laboratory participates in the development and revision of air quality criteria documents on pollutants for which national ambient air quality standards exist or are proposed, provides the data for registration of new pesticides or proposed suspension of those already in use, conducts research on hazardous and toxic materials, and is primarily responsible for providing the health basis for non-ionizing radiation standards. Direct support to the regulatory function of the Agency is provided in the form of expert testimony and preparation of affidavits as well as expert advice to the Administrator to assure the adequacy of health care and surveillance of persons having suffered imminent and substantial endangerment of their health.

This report addresses the identification of gaps in current knowledge, identification of research that needs to be performed to fill these gaps, and determination of research with a high probability of clearly examining the health effects of particulates.

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-Investigation of stomach cancer in relation to airborne particles is recommended

-Adequate exposure estimates must be made

-Quality assurance/control of all measurements is very important

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INTRODUCTION

The members of the Workshop on Epidemiologic Studies of Airborne Particles have met to assist the EPA in determining the research needed to meet the present and future research requirements of the Environmental Protection Agency in this field. This goal was accomplished by identification of gaps in current knowledge, identification of research that needs to be performed to fill these gaps and determination of research that the workshop members believe has a high probability of success.

Despite more than a decade of research, knowledge relating human disease to air pollutants is still incomplete. The question of primary interest to epidemiologists is: "What is the disease risk for a given level of exposure to a population?" This is the implicit question that needs to be answered for inhaled particles, but the panel agreed that before this question could be successfully addressed and meaningful studies performed, our knowledge of what to measure in the air and in human subjects, and which groups to measure, had to be evaluated. It was evident that there were serious flaws in previous research in the area of particulate pollution. Some of these flaws included inadequate methods and the use of incomplete data sets; either exposure measurements and/or the measurements of disease endpoints were inadequate, resulting in improper conclusions.

The research areas that were explored and considered to be of prime concern in future research in studying possible health effects of airborne particles may be outlined as follows:

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1. Particle Characterization

   a. Determination of particle size range to study

   b. Necessary degree of characterization of chemical and physical properties

   c. Degree of chemical and physical uniformity of particles required for studies in different cities or areas

2. Sampling Methods

   a. Types of devices

   b. Location and frequency of sampling

   c. Continuous and intermittent sampling

   d. Reliability in field applications

3. Quality Assurance/Control of Air Measurements

   a. Instrumental performance

   b. Independent comparisons

   c. Commitment of resources

4. Exposure Assessment

   a. Correlation of personal exposures and ambient measurements

   b. Exposure measurements and lung doses

   c. Quantitative comparison of ambient and occupational or home sources

   d. Usefulness of dose markers

5. Disease Endpoints to be Studied

   a. Respiratory disease

   b. Cardiovascular disease

   c. Cancer

   d. Other

   e. Morbidity vs mortality

   f. Acute vs chronic effects

   g. Confounding factors

6. Design of Health Effects Studies

   a. Design requirements for particular health endpoints

   b. Statistical methodology and limitations

   c. Evaluation of special populations at risk

   d. Quality control in health evaluation.

We now consider these topics in some detail, with emphasis on those technical issues that have formed the basis of our recommendations.

Particle Characterization:

A wide range of particle sizes should be studied; less than 2.5 μm, between 2.5 and 15 μm, and particles larger than 15 μm. It was felt that specific irritant or other effects on the upper and lower respiratory tract, as well as physiologic effects on other organs may be dependent on the whole range of the particle
* size spectrum. For this reason, monitoring should be designed for each study depending on the endpoint, but because it may be difficult to predict the biologic endpoint anticipated the size range should not be limited at the outset. In any case, simplicity and reliability of the measurements of particle size distribution is important in study design. Because the EPA dichotomous samplers have been developed to assess particle size distribution and are already available, they may have to be the primary base for some current measurements, but there was concern by workshop members that the dichotomous samplers were too limiting (did not measure the larger sizes) or may be unduly sensitive to wind direction. The
* problem of an appropriate field measuring device for sizing airborne particles was considered to be important in future research planning.

Characterization of physical or chemical properties of particles could be important, especially if studies of different cities are compared. It does not
* appear realistic, however, to do community studies relating specific disease

endpoints to the numerous possible constituents in the particulate phase, and in this instance total airborne particles are of principal concern. In special cases it may be possible to measure specific disease endpoints in relation to a particular chemical composition of the particles of ambient air when there is a plausible biological basis for suspecting that the chemical fraction may be related to a disease. A related question is how similar chemically or in terms of size range the mix of particles in one area or city under study has to be to another in order to permit comparisons of health status to be meaningful. This is an area * of research needs that EPA has begun to address, and more work will be required to establish the similarity or lack of similarity of airborne particle distributions from area to area and region to region.

Sampling Methods:

The types of measuring devices available will have considerable impact on sampling strategies but the appropriate device may in turn be determined by the hypothesis being tested. Obviously, if characterization of a number of complex chemical constituents is necessary to evaluate the effect of exposure on a particular disease, the extent of a monitoring network may be sharply limited by logistic considerations.

The location and frequency of sampling may be critical to the adequacy of * defining exposure in a study. Determination of the monitoring requirements of each study community should be done before any study is initiated; these should conform to the study design, established by the hypothesis being tested. Although these points are generally acknowledged, there has been little or no documentation to show that monitoring is being done adequately, i.e., if the numbers of monitors being used in communities are justified, if the measurements are a true indicator of community exposure, or if the measurements are being taken adequately to

measure the variability in levels with space and time. The need to sample at a certain frequency and for a given duration should also be well documented, for
* example, whether continuous or intermittent sampling is appropriate. We recommend that EPA and the investigators should carefully develop monitoring strategies in any future studies.

The reliability of any field sampling methods needs to be thoroughly established. In the past, laboratory models for measuring air pollutants have been deployed in the field without sufficiently qualified personnel to operate them and without an awareness of technical requirements for maintenance of accurate measurements.

Aerometric monitoring in epidemiology should provide accurate estimates of individual and population exposures to pollution. The criteria for site selection, frequency of sampling, instrumentation and filter media, subsequent chemical
* analysis, and data management must be considered in establishing a comprehensive air monitoring system.

Quality Assurance/Control of Air Measurements:

Precision and accuracy of measurements must be documented in a quality assurance program, with checks of different sampling sites and study areas that are sufficiently detailed to permit assessment of the reliability of inter-regional comparisons. The first aspect of quality assurance is determining reliability of instrumental performance, including the capability and performance of technical staff responsible for deployment and maintenance of the equipment and collection of results. The suitability and reliability for routine field use of instruments developed in the laboratory should be thoroughly determined before they are accepted for epidemiologic study purposes.

Independent comparisons of results obtained by duplicate "blind" sampling procedures in a certified reference laboratory and with the field equipment is the

heart of a quality assurance program. It is preferable if the method used in the reference laboratory involves an analytical technique that is not identical with that of the field method. Sampling and chemical and physical analysis of particles in selected size ranges have not yet been standardized, and therefore protocols for quality assurance will have to be developed.

Because of the crucial importance of quality assurance in the success of any epidemiologic study of health effects of airborne particles, adequate commitment
* of resources for this purpose is mandatory. The workshop members recommend that up to 30% of the direct costs for air monitoring should be allocated to quality assurance. Detailed quality assurance procedures for standard (direct and equivalent reference methods) monitoring have been developed by the Quality Assurance Division of EPA and other groups involved in air monitoring. For airborne particles independent calibration and performance audits for experimental instruments and methods are not now readily available.

Exposure Assessment:

Evaluation of the correlation of personal exposures and ambient measurements of airborne particles will require additional studies to be designed. To undertake personal exposure monitoring as part of epidemiological investigations of effects of airborne particles will be expensive. Field experience has indicated that personal monitoring studies are labor intensive, limited in full representativeness of population and are restrained by the quality of available instrumentation. To develop personal monitoring suitable for full scale epidemiologic studies,
* sampling equipment should be improved to make it lightweight, and collect particulate mass in sufficient quantities for precise and accurate mass, chemical, and element determinations.

Ultimately the purpose of exposure assessment is to permit exposure measurements to be related to lung doses of total particulate mass inhaled or from specific chemical components. This kind of information must be supplied primarily by theoretical or laboratory investigations, but it is important to recognize that physiological factors related to respiratory characteristics of the populations under study will be important parameters determining the relationship of exposure to dose. Thus, for example, body size, age, or the presence of pre-existing disease may modify the ultimate dose, and may be major determinants of special populations at risk.

Quantitative comparison of outdoor ambient sources and occupational or home sources of exposure will be important to carry out. It is conceivable that indoor exposures to airborne particles at home or at work may contribute very significantly to the total population exposure. Strategies for personal monitoring will have * to take this possibility into account in order to be able to assess the relative importance of indoor and outdoor sources.

Because exposure assessment from air sampling alone is complex and subject to important questions, some measure of exposure based on monitoring of members of the study population, using dose markers obtained by biological testing, could be very useful. In the case of airborne particles, such markers are not yet developed, and further research will be required, but it is research that could result in major advances in evaluation of health effects from inhaled airborne particles. The presence of gaseous constituents in community air should be measured along with the particulate component. Photochemical oxidant will be especially important because in some experimental designs we suggest that photochemical oxidant be studied as an independent variable. Sulfur dioxide should also be measured because of historical interest in relation to airborne particles.

Disease Endpoints to be Studied:

The workshop devoted considerable time and effort in evaluating the relative importance of individual categories of disease as subjects of study of health effects of airborne particles. By means of a rating system, priorities were assigned to specific disease endpoints. The decision to assign a rating to each of the areas of study was based on several points of discussion: 1) biological plausibility relating particulate pollution to the disease; 2) current experimental and epidemiologic evidence; 3) potential relative contribution of other etiologic or risk factors, and 4) quality of previous epidemiologic studies.

To facilitate in the decision making, each of the disease categories, as well as specific areas of study, was agreed upon (Table 1). A score of 0 to 5 was assigned by each panel member to each category, as an indicator of the need for future research. The basis for these individual ratings was the experience and judgment of the workshop participants. (Score: 0 = not worth doing; 5 = highest priority). Four areas emerged that were given special weight in terms of effects of airborne particles. These were: 1) acute and chronic respiratory disease morbidity, including infectious disease of the upper and lower respiratory tract, and respiratory disease mortality; 2) cardiovascular disease morbidity and mortality (acute effects); 3) gastric cancer, and 4) behavioral effects associated with exposure to particles. In general there was good agreement among the panelists about these priorities. In the following discussion, the basis for the decisions reached and some details about the endpoints within the large categories to be emphasized is presented.

Acute Respiratory Disease Morbidity:

Acute respiratory disease may be divided, for convenience, into a few categories: Those resulting from irritant reactions alone, those with an infectious component,

TABLE 1

Rating of priorities for disease categories to be evaluated in studies of health effects of airborne particles

Workshop Panelist	RESPIRATORY DISEASE					CARDIO-VASCULAR		CANCER					MISCELLANEOUS			
	Chronic	Acute	Infectious	Structural Change	Mortality	Morbidity	Mortality	Gastric	Lung	Naso-Pharynx	Prostate	Other	Reproductive	Cirrhosis Diabetes Hematology	Behavioral Changes	Neurologic Sensory
1	4	5	4	1	2	5	5	4	2	1	1	0	2	1	3	3
2	4	5	4	1	3	2	2	3	2	1	1	1	3	0	2	0
3	5	5	1	3	4	5	2	3	0	0	1	0	3	0	3	0
4	4	5	0	0	2	3	3	0	0	1	0	0	0	0	3	0
5	5	5	0	0	3	4	5	4	1	2	0	0	2	0	4	3
6	5	4	2	3	1	3	1	5	3	0	4	1	5	2	3	4
7	5	3	0	0	4	5	3	3	0	0	0	0	1	1	1	0
8	5	5	2	1	2	2	1	0	1	0	0	0	0	0	3	0
9	5	5	4	3	2	4	3	4	2	1	1	1	3	1	3	3
TOTAL	42	42	17	12	23	33	25	26	11	6	8	3	19	5	25	13

Rating scale: 5 = highest priority; 0 = lowest priority

those with an atopic or allergic component, and those of various natures which occur in patients with pre-existing disease. Particles are believed to play a role affecting the onset and course of various acute respiratory diseases. However, this potential effect needs further study and the following points need to be addressed: 1) The size and speciation of the particles which may produce or exacerbate acute respiratory disease; 2) the importance of acute respiratory disease in the development of chronic respiratory diseases; 3) the nature of high, short-term exposures associated with acute respiratory diseases, and 4) the effect of long-term exposure to relatively low levels. The characterization of important convariables requires more work; these include, for example, meteorological factors, temperature, and exposure to aero-allergens or epidemic viruses, all of which may have an effect greater than exposure to particles.

Other factors that must be considered are other pollutants (indoor and outdoor), smoking, occupational exposures, recreational exposures, and infectious agents. Other confounding variables of importance include: Housing characteristics, socio-economic status (especially education), and factors which may determine individual sensitivity or susceptibility. These include immunologic status, familial history of respiratory disease and previous acute respiratory history, including asthma or chronic bronchitis.

Studies of acute respiratory effects of inhaled particles include as an important element the topic of respiratory infection, both conceptually and in practical terms. Conceptually, increasing evidence suggests both that exposure to air pollution (including particles) promotes lower respiratory infection in childhood, and that childhood respiratory infection predisposes to chronic respiratory illness later in life. If this concept can be further elaborated, then infection is an important outcome variable in epidemiologic studies of air pollution.

Further evidence indicates that the distribution of infectious agents varies widely in time and space, and that the severity of acute illness and its long-term sequelae varies with different infectious agents. Also, toxicologic studies show that different pollutants exert different effects on infectivity. These findings also indicate that infection is an important covariate in studies of pollution, and must be controlled for, especially when studies are conducted in different communities.

Thus, in studies of air pollution and acute respiratory disease, it is desirable to characterize respiratory infection both in individual subjects and in their communities. On a practical level, however, these desirable goals may be very difficult to achieve, since detection methods are rather insensitive and quite expensive. Thus, in planning for studies of acute respiratory disease, the desirability of characterizing the impact of respiratory infection should be carefully balanced against the practical difficulties of doing so.

Chronic Respiratory Disease:

Previous research indicates that airborne particles, alone or with sulfur oxides, contribute to the prevalence of chronic airway obstructive disease. It appears to contribute also to exacerbations in such disease. At present, it is unclear still at what exposure levels these occur, what particle sizes are most important, and what is the chemical nature of the particles which may have such effects. Furthermore, the nature of the problem in sensitive individuals (e.g., asthmatics) and in less susceptible invididuals, is unclear. Finally, the mechanisms associated with various effects need further research, again, in part, in relation to the irritant or specific chemical nature of the particles. Problems which need to be overcome in such work include: 1) Development of adequate monitoring and methods of analysis; 2) determination of actual exposure and dose cumulatively for

individuals; 3) determination of interactions between particles and gases, cigarette smoke, pollen, etc.; 4) determination of relative effects of high, short-term exposure and low, long-term exposure, and 5) determination of the constituents of susceptibility and/or resistence.

One approach to studying effects of air pollution on chronic respiratory diseases has been through studying geographic variations of mortality statistics. These studies have attempted to attribute excess deaths between different populations to different levels of pollution in defined geographic areas. The basic problems with such studies are that ascertainment of numerator data for mortality statistics has been incomplete, exposure or dose of the pollutant(s) to populations is often unknown, and other environmental factors (smoking and occupation) have not been adequately controlled. Though mortality is a well defined endpoint, death rates from chronic obstructive pulmonary disease (COPD) have been less than adequate for epidemiologic purposes. The limitations result from a number of factors. Standard criteria for diagnosing the disease have not existed until fairly recently, and different standards in medical practice may bias certification of death. Even when the disease is diagnosed according to established standards and criteria, assignment of the cause of death is often inadequate for epidemiological purposes because the cause of death assigned may differ either because of the certifying physician or in the coding of the death certificate. Local practices in the departments of vital statistics for coding the underlying cause of death differ, and changes in the ICDA codes between revisions complicate comparisons over time.

For the above reasons, incomplete and biased ascertainment of numerator data is a serious problem when mortality statistics are used for geographic comparisons of nonmalignant respiratory diseases. The largest component of this aspect of the problem, at least in the United States, is the existence of con-

comitant chronic conditions (heart disease and pneumonia), that by convention are coded first. The coexistence of heart disease and COPD will probably be coded as heart disease at the time of death. For example, Moriyama reported in a study of death certificates that COPD is often omitted as a contributing cause of death (1). In a study of more than 350 autopsies, Mitchell noted that the disease often goes unreported and that emphysema was found to be unassociated with severe clinical airway obstruction. In an autopsy study(2) he found that 78.2 percent of 101 individuals who died of chronic airway obstruction died from emphysema or chronic bronchitis, 22 others of heart disease and the remaining 18 from other causes.

When the components of COPD (chronic bronchitis, emphysema, and asthma) are considered separately, the picture becomes further complicated because there are several diseases to consider, all presenting similar clinical symptomatology, all of which are subject to the same problems of ascertainment and assignment of the cause of death. The geographic comparisons of mortality rates between countries are severely restricted by the problems listed above, especially by differences in the certification of the cause of death. This seems to be one of the principal reasons for the fact that chronic bronchitis death rates are several times higher in Great Britain than in the U.S. (3).

Urban-rural mortality differences from chronic respiratory disease have been noted in Great Britain as well as in the United States (4). Almost all of these differences have been attributed to socio-economic differences. The higher rates among the lowest social strata, as measured by differing occupational, educational or income classes, were attributable to differences in smoking habits. For all these reasons, the workshop participants felt that respiratory mortality studies had to be coordinated with morbidity evaluation.

Geographical studies of morbidity from COPD in the U.S. and Great Britain have shown the same pattern as mortality statistics. Urban areas or more densely populated areas have rates nearly double rural areas, but again, the relationship between level of pollution and COPD morbidity is uncertain. An inverse relationship between income level and respiratory disease has also been found in these studies. Several surveys have suggested that the prevalence of respiratory symptoms and COPD may be higher in the less educated (4). Due to the striking dose-response relationship between COPD and cigarette smoking, and the social class gradient for smoking seen in geographic studies both in the United States and Great Britain, such studies must take account of smoking differences between populations. Perhaps a better analysis of chronic bronchitis might be accomplished in a population of never-smokers exposed to different levels of pollutants in different geographic areas.

For the study of the etiology of chronic obstructive pulmonary disease, the most fruitful approach, therefore, is a longitudinal study in which known factors are examined over time in relation to the onset and cause of COPD. These factors would include: Smoking, familial history, atopy, childhood respiratory infection, occupation, home factors, socio-economic status, and exposures to pollutants by size and speciation since birth (with estimates for exposures prior to the study). This probably requires complete residential and occupational histories, family trees, etc., with some retrospective determination of these variables. The study would require atmospheric and biological monitoring, as well as adequate monitoring of pulmonary function, atopy, and changes in key factors, and would require adequate determinations of symptom/disease states. Sources of genetic and environmental determinants of susceptibility should be sought. Monitoring of sensitive individuals should be necessary, especially during episodes of high particulate pollution. The study should take place in an area with variable particulate levels (and

possibly where sub-areas have different levels). Such studies should be performed in areas with different types of particles such as from fossil fuel combustion, fugitive dust, or specific industrial operations.

Cardiovascular Disease. Chronic:

Effects of particles on chronic cardiovascular disease are difficult to measure, much harder to study, and are less likely to be worthwhile, primarily because detection of asymptomatic chronic disease is so incomplete. At this particular time, the panel agreed that efforts to evaluate cardiovascular disease should stress acute and not chronic effects, unless a very specific disease such as myocarditis is being related to a chemical pollutant in a special environment.

Acute:

Acute cardiovascular effects include precipitation of congestive heart failure, angina pectoris, and sudden death from myocardial infarction. It is often very difficult to define the underlying cause of death because of concomitant cardiac and respiratory failure at the time of death. Many people who have chronic respiratory disease die supposedly of cardiovascular disease. They develop some heart disease or apparent heart disease. Physicians, unfortunately, still have difficulty in telling whether shortness of breath is related to pulmonary disease or to congestive heart failure.

An argument might be that the most susceptible population in terms of respiratory effects of airborne particles may be patients who have congestive heart failure and not patients who have modest reduction of pulmonary function. In the former case, death may ensue through a respiratory mechanism. The effect that can be measured may be the precipitation of congestive heart failure. Therefore, a logical study design might be to look at patients with congestive heart failure, find out whether changes in pollution have resulted in acute episodes of congestive

heart failure, and measure pulmonary function as related to the episode.

Cardiovascular - Respiratory Disease:

It was agreed and strongly recommended by the panel that cardiovascular disease and respiratory disease should be studied collectively. There were several reasons for this decision. First, the pathophysiology of acute cardiovascular failure and respiratory failure is not clear. It is often very difficult to define the underlying cause of death, because of concomitant cardiac and respiratory failure at the time of death. Many people who have chronic respiratory disease are reported to die of cardiovascular disease.

Secondly, most of the workshop members were convinced that a variety of single isolated studies to look at the problem of cardio-respiratory effects of inhalable particles, studies which were not clearly integrated would have relatively little chance of success, and that a more standardized study which could look at several specific disease groups using the same populations and data collection techniques has the best potential for defining the problem.

In the research plan described in the appendix, the panel has recommended
* that acute effects of airborne particles on cardiovascular disease be studied together with the acute and chronic effects on acute and chronic respiratory diseases. This would be a collaborative community study in which different health parameters would be evaluated within age and sex groups.

Cancer:

With the recognition that chemical carcinogenesis was an important causal mechanism for neoplastic disease, there arose interest in the investigation of populations exposed to airborne agents. This led to studies of occupational settings, and community investigations of air pollution. Ecological studies in England and Wales showed associations between particulate pollution and mortality

from lung, prostate, and bladder cancer (5). The demonstration of an excess risk between cigarette smoking and lung cancer during the 1950s stimulated further interest of the relationship between lung cancer and air pollution.

Lung cancer has been of great concern because it has been the leading cancer in men, accounting for over thirty percent of all cancers. In women, it is expected soon to become the leading cancer as well. Excesses in lung cancer mortality have been seen in urban populations (6). It has been suggested that a positive relationship exists between lung cancer mortality rates and pollution levels, and an inverse relationship between the disease and social class (7). Studies have also demonstrated a strong social class gradient for smoking consistent with the socio-economic distribution of the disease (8). Because of the large attributable risk due to cigarette smoking (80-90%), smoking differences among residents of different geographic areas account for almost all of the differences in lung cancer risk observed between the areas (9). For these reasons, the panel concluded that study of lung cancer in relation to airborne particles was not likely to be fruitful and thus was not of high priority.

Bladder cancer, prostatic, and stomach cancer have been found to be associated with particulate pollution. In Nashville, all three cancers were associated (10), while in Buffalo, stomach and prostate were associated (11). The biological plausibility for a relationship of prostatic cancer to air pollution is based on a few inconclusive studies of occupational groups exposed to cadmium metal or compounds of cadmium. The present evidence is insufficient, however, to warrant major research efforts at this time.

For stomach cancer, however, the biological and epidemiological evidence supports a possible causal relationship between particulate pollution and the disease. The panel concluded that priority should be given to an investigation of the relationship between stomach cancer and particulate pollution.

The relationship between stomach cancer and possible exposure to non-respirable particulate pollution from the burning of coal is of great potential importance. If the burning of coal is increased, as expected, and major emphasis is on the reduction of fine particles, it is conceivable that the rapid decline in stomach cancer may stop and there may even be an increase. The evidence for a relationship between particulate pollution and stomach cancer rests on the following five sets of observations:

1. In urban areas, i.e., Buffalo and Nashville, previous studies have shown that stomach cancer deaths are directly related to particles even after adjustment for social class and ethnicity (11).

2. The sharp decline in stomach cancer death rates parallels, with a lag of 10 to 20 years, the decrease in per capita coal consumption and in total airborne particle levels.

3. Coal miners in the United States, England and Wales have increased stomach cancer death rates. Stomach cancer is the only cancer which is substantially elevated among coal miners (12).

4. Stomach cancer death rates are higher in areas of Western Pennsylvania which apparently have high concentrations of coal mining and also perhaps coal burning (13).

5. There is also evidence that there are specific carcinogens in insoluble particulate pollution from coal burning, and that most of these would be expected to be swallowed.

This evidence needs further clarification. The elevated rates among coal miners in different parts of the world appear to be real. The environmental factors responsible for the excess mortality, though, are not clear.

It is generally believed that the ingestion of certain chemicals or chemically contaminated foods can result in the transformation of healthy gastric mucosa into malignant tissue. This idea has been supported by descriptive epidemiological studies and by several analytical studies. However, it is unclear as to what chemicals are responsible for the unique distribution of the disease. The need exists for well defined studies to clarify which environmental agent(s) are

significantly associated with stomach cancer, especially in coal mining areas.

Because of the long latent period for stomach cancer, it would not be feasible to study disease risks prospectively. Retrospective studies in areas of very high risk and/or low risk may reveal associations between incidence and particulate exposure or other factors. Research should also be continued experimentally using animal models. Currently, the Center for Environmental Epidemiology at the University of Pittsburgh is undertaking a case-control retrospective study of stomach cancer in southwestern Pennsylvania, a high risk area of the United States.

Ecological studies, i.e., studies examining the geographic distributions of diseases in populations according to various characteristics, are usually denigrated with respect to their usefulness for testing causal hypotheses. This is because such studies frequently employ data which are not directly ascertained from the case population. For example, in ecological studies of mortality and air pollution, many of the characteristics of cases, as well as their air pollution exposures, are determined from data for census tract of residence at time of death. The characteristics of the cases may not be the same as those of the census tract population. Such a situation may give rise to so-called ecological fallacies.

In spite of these criticisms, ecological studies have proved to be of value, especially when followed by case-control studies. They are frequently the only available approach to the study and understanding of community-wide epidemiological phenomena. The results of ecological studies have led to the development of etiological hypotheses, have been useful in validating hypotheses, and are frequently the basis for planning and evaluating health services. They are often the necessary precursors for the design of more direct analytical investigations.

Thus, the panel recommends consideration of two types of ecological studies;
* cross section and prospective, for the investigation of a possible causal association(s)
* between exposure tc airborne particles and stomach cancer. It also recommends the use of case-control studies for measuring the strength of the association with all cancers and for determining any spurious associations.

Cross-sectional studies examine the geographic distribution of the occurrence of stomach cancer at some period of time and compare this distribution with the distribution of air pollution either at the time of occurrence of disease or at some other time (assuming that the distribution of pollution has not changed in a major way over time). Co-variables such as age, race, sex, ethnicity, occupation, and socio-economic status are also considered. As indicated previously, such cross-sectional studies carried out in the late fifties and early sixties in this
* country showed an association between suspended particulate pollution and stomach cancer. These studies should be repeated taking advantage of improved quality of available data. Some possible avenues are:

1. Studies in communities where Third National Cancer Survey (TNCS) was carried out.

   The TNCS was the most careful ascertainment of cancer incidence ever carried out. Since it encompassed a census year, 1970, rates derived from it are considered particularly valid. The cases were identified by census tract of residence and a survey of a sample of cases obtained additional information on personal characteristics of cases, so that the data provide an unusual opportunity for community-wide studies. In the TNCS communities for which good air pollution data exist, rigorous cross-sectional ecological studies of stomach cancer incidence should be carried out.

2. Studies in communities where good air pollution data are available.

   Several large communities known to have good air pollution information should be identified. In these communities, mortality studies should be organized. Since the case fatality ratio for stomach cancer is very high, mortality studies are satisfactory. Rigorous mortality studies can be conducted economically provided the communities selected can provide some cooperation.

3. An additional useful approach is the identification of geographic areas with very high and low incidence and mortality rates for stomach cancer followed by an investigation of factors that may explain the distributions.

Prospective studies usually connote classical cohort investigations in which a population is divided into those with and those without exposure to a putative causal factor, and the study population is followed forward through time so that the differential occurrence of disease in the two groups may be evaluated (relative risk). Since changes in air pollution characteristics are accompanied by so many other changes, attributing causation to the air pollution component of change is often difficult. Nevertheless, if some component of air pollution is causally related to a disease, the fluctuations of factor and disease occurrence should be harmonic. Such a relationship will be greatly strengthened if it is predicted in advance. The panel recommends two types of prospective study; community-wide surveillance and special studies of populations exposed to point sources of particulate pollution.

a. Community studies

The EPA should designate several urban and rural areas of the United States as special disease and environmental surveillance areas. These communities should be chosen from both stomach cancer and pollution communities with a history of monitoring. In these communities, special disease ascertainment, extended census taking, and environmental monitoring should be undertaken. These communities might then serve as sentinels for early identification of environmental effects, both good and bad.

b. Special power source studies

Power sources (of all types) which are relatively isolated from other industries or which are known to be the dominant pollution of some defined population should be identified and surveillance systems for a variety of diseases should be established among the exposed population.

Case-control studies are effective strategies for identifying environmental factors in disease. Although they are usually considered less rigorous than prospective studies, there are very few examples of associations demonstrated in good retrospective studies turning out to be spurious in subsequent prospective investigation. Thus, the panel recommends that case-control studies of stomach

cancer, and indeed such studies of any neoplastic diseases which are suspected of being environmentally influenced, contain provision for collection of information on occupational experience and residential location.

Behavioral or psychological effects of airborne particles:

The types of effects involved here include annoyance reactions, preference-avoidance reactions, or responses to such factors as decreased visibility, crop damage, effects of acid rain, or esthetic changes. These involve endpoints for which individual or group measurement techniques are as yet not well developed for airborne particles. Indeed the panel concluded that it is probable that any initial studies proposed in this area should be directed toward evaluating measurement instruments, such as psychological scaling tests or questionnaire methods. While there was agreement that this area of research was important for EPA, the panel did not consider that it was sufficiently expert in these problems to make definitive recommendations for research at this time. The panel * recommended that EPA convene a workshop of persons well-qualified in this general area of research, including psychologists, sociologists and possible economists, all familiar with field survey methodology to consider research strategies. Included in such a workshop should be some individuals expert in air pollution measurement. The problem area could extend to other pollutants than airborne particles or sulfur oxides.

Reproductive effects:

The need to look at reproductive effects and birth outcome was expressed by the panel. However, at the present time, there does not appear to be a good model for studying how particulate pollution could affect the gonads, how best to measure the dose, and which biological effects should be measured.

The panel felt it could not design a good study to look at reproductive

effects of particles, given the current knowledge of the state of the art.

* The panel recommendation was to refer this problem to other agencies, perhaps in NIH, to address research specifically to the role of pollution on reproductive effects.

Design of health effects studies:

The requirements for study designs appropriate to investigation of any environmental pollutant will depend on the nature of the pollutant, the route of exposure of human populations, the disease process suspected of being involved, and whether that process shows acute or chronic manifestations. Thus it is not possible nor would it be wise to stipulate a single optimum design for studies of possible health effects of airborne particles. In the case of cardio-respiratory disease, the proposal is for a multi-community prospective study. In the case of

* stomach cancer, geographical and occupational studies were recommended along with a case-control evaluation of the strength of association. Behavioral effects of airborne particles will obviously require different designs.

Statistical methodology is available in theory for the proper testing of

* the null hypothesis. Selection and adaptation of existing methods to a practical situation should be made in light of the following points of caution:

1. Conformity to underlying assumptions

   In recent years, the availability of statistical computer package programs has made the application of different statistical techniques to practical problems much easier with less risk of being misused by people with little or no knowledge of statistical theory. Conformity of the data to underlying assumptions of a selected statistical technique is absolutely necessary before the data are subjected to that analysis. In case some robust procedures are selected, conditions for robustness and also degree of robustness should be properly addressed.

2. Inadequacy of regression analysis

   When many possible outcome determinants are present, not only is inference difficult, but spurious association is likely to occur.

This is due to the fact that the correct determinants are rarely identified fully and accurately and the hypothetical determinants that are examined serve only as surrogates for the correct ones. It is for this reason that associations drawn from regression analysis should not be considered as demonstrations of causality. Rather they are useful only in the context of a larger body of information.

3. Problems with weak effects

The difficulties of regression and correlation analysis are exacerbated in dealing with a hypothetical determinant, such as particles, which may account for a minor portion of a health measure. The presence of certain systematic associations between air pollution levels and strong forces affecting mortality and morbidity will cause positive associations between air pollution and adverse health measures. The association will persist regardless of the absolute pollution level.

4. Problems with multiple comparisons

When a large number of tests of significance are performed in a statistical analysis, a number of significant results can occur solely due to chance. Awareness of the problems arising from multiple comparisons is needed in evaluating any significant finding.

5. Importance of covariate controls in area studies

Because area studies are specially vulnerable to covariate influences, it is extremely important to control properly the strong factors affecting the health measures being examined. For example, studies addressing stomach cancer should include nutritional patterns.

6. Problems with colinear variables

A review of the literature of epidemiologic studies of health effects of atmospheric pollution shows us the limitations of such studies in separating the effects of a particular compound from the effects of other pollutants and smoking. Future research should give careful attention to complications arising from correlated variables.

Evaluation of special populations at risk may be an important secondary aim of epidemiologic research, when there is a good biological basis for selection of these populations in advance. Some host factors that may be important in evaluating disease related to airborne particles have already been mentioned. These include age and preexisting cardiovascular or respiratory disease, as well as ethnic characteristics that can be associated with diet or lifestyle.

Quality control in health evaluation is at least as important as in air monitoring, especially if several clinical centers are cooperating in a multi-
* center study. In this case, however, not only are accuracy and precision of laboratory procedures important, but the qualifications and techniques employed by clinical personnel may become especially of concern.

Appendix

Summary of a research plan for investigating the relationship of cardiorespiratory disease to exposure to inhaled particles.

The most feasible plan to study the potential health effects of inhaled particles is a collaborative community study in which several different health parameters would be evaluated within age and disease specific groups, and with race and sex possibly also investigated. As mentioned already, the workshop members believe that study of both pulmonary and cardiovascular morbidity and mortality should be combined in the study design and the analysis of the data. In what follows, the selection criteria used for study communities is often based on cardiovascular disease mortality rates because these are both available and reasonably reliable, but the aim is to use a variety of health endpoints in evaluating possible effects of different levels of exposure to airborne particles.

Two particular types of study design were considered: 1) A study of airborne particles related to burning of coal. In this model, the communities would be selected in relationship to the current total suspended particles (TSP) into high, intermediate, and low values, and then further sub-classified on the vertical axis into high, intermediate, and low cardiovascular disease mortality. This would result in a nine community study. 2) The second model would evaluate TSP and also variation in oxidant levels. In this case, TSP would also be divided into a high, intermediate, and low community and within each of the TSP groupings there would be a high and low oxidant. The mortality grouping would be divided into two strata, a high mortality community and a low mortality community from cardiovascular and respiratory diseases predominantly in the 45-64 age group.

These studies would be able to do the following: First would be to determine whether there are differences in a variety of physiological parameters, mainly pulmonary function and evidence of chronic obstructive pulmonary disease in the

communities with levels of pollution high as compared to the intermediate or less polluted community. Second, would be to determine whether the chemical and physical characteristics of the airborne particles in the high pollution, low mortality community, are similar to those in the high pollution, high mortality community, and whether there were differences in the small particle component compared to total particles between the high mortality, high TSP community and the high mortality, low TSP community.

There was some debate about whether three levels of exposure were necessary, that is, high, intermediate, and low. In general, it would be preferable to have an intermediate point in many of the analyses. The basic hypotheses to be tested probably relate to the smaller particles, their amount, physical and chemical characteristics rather than to total suspended particulates. Furthermore we believe that an important measure in relationship to cardiovascular and pulmonary disease would be variation in incidence of new events or hospitalization over a specific time in relationship to changes in pollution levels within each of the high, intermediate and low polluted communities. Thus, the overall rate will be of less importance than the temporal and spatial distribution of cases within the community in relationship to pollution levels.

Some of the characteristics of the community were also defined, such as size. The communities should probably be no greater than about 100,000 people; however, they could be a sub-division of a larger area as long as the population within the sub-community can be clearly defined in relationship to their work status, housing, sources of medical care and pollution exposures. Probably a census tract or group of census tracts within a large city should be avoided since it would be extremely difficult to relate the pollution level to the mobile population in terms of jobs, recreation, etc. The population should be relatively stable since some of the study designs require longitudinal follow-up and loss of population to follow up could have great effects in evaluating the results.

Confounding by unusual job exposures, such as half the population being involved in coal mining, should obviously be avoided. Ideally, there should be some variability of pollutant levels over time within the community.

Several situations were considered: 1) Communities where the pollution levels are currently low, but where, if a power plant is constructed, one can anticipate that in the next few years the pollution level will rise, that is, going from low to high levels of airborne particles. 2) Areas where the pollution level now may be high but there is anticipation that because of control technology the levels will be substantially reduced in the future. If such communities can be identified, they would be ideal for this model since the basic background information, that is, the cross-sectional information, could be collected prior to the changes and then the changes evaluated. Furthermore, even in those communities where there is not a major change it would be preferable to select communities where some variation over time has occurred. This would improve the likelihood of being able to measure variations in hospital admissions from cardio-pulmonary disease or mortality, as well as the potential for doing panel studies to determine the effects of acute changes in respiratory function in relationship to changes in pollution in both the high, intermediate, and low polluted areas.

There was some debate, never completely resolved, of whether the pollutant sources within the community should be well-defined so that the characteristics of the pollutants themselves and the potential for modification in the future can be evaluated. Furthermore, it was agreed that air pollutants other than inhalable particles should be measured, and that a carefully evaluated air monitoring system must be available. There should be a history of previous pollution measures within the community and the prior measurements should be reasonably good. In general, wide variation in the types of sources of airborne particles should be avoided.

The study design that was proposed was the identification of population sample within each area. This would consist of a sample of children, adults, and the elderly. Two approaches to evaluation of respiratory disease would be followed: First, longitudinal studies consisting of basic pulmonary function. The minimal tests would include pulmonary function which must comply with the A.T.S. Snowbird Conference criteria on epidemiology (14) and in Ferris' Epidemiology Standardization Project (15). Minimal pulmonary function tests must include an FEV_1 and FVC. Other measurements may also be used as indicated as well as more detailed pulmonary function measurements in certain selected sub-groups. Standard respiratory questionnaires must also be used at all sites. The examples for adults and children are presented in the Epidemiology Standardization Project (15). Additional questionnaires may be used but should conform with the recommendations in that report. Second, demographic and medical information should be available and occupational history included.

There was some debate whether yearly examinations were required. The group felt that this would have to be discussed in relationship to cost feasibility and yield from yearly examinations. Besides the longitudinal studies it was felt that special sub-studies should be done on high risk populations within each community. This might include individuals with decreased pulmonary function, those who have specific clinical diseases, and sub-groups of smokers and non-smokers with abnormal pulmonary function measurements. Furthermore, it was proposed that at least one sub-group panel study be done to measure the acute changes in pulmonary function in relationship to anticiapted changes in airborne particles within the communities.

Cardiovascular evaluation should include the following studies: 1) An initial evaluation of arteriosclerotic heart disease, chronic obstructive pulmonary disease, and total mortality rates within each of the communities. 2) Measurements of cases hospitalized for acute myocardial infarction based on review of

hospital records including electrocardiograms, enzymes and symptomatology. Sub-classification of hospitalized myocardial infarction and cardiovascular disease patients to various sub-groups but specifically into those who have incident myocardial infarctions (transmural and non-transmural). 3) Surveillance of all cardiovascular admissions to the hospitals in the community, all deaths and especially sudeen deaths with follow-back interviews for the sudden deaths and perhaps for total deaths within the community. 4) Surveillance of all patients with chronic obstructive pulmonary disease and also an evaluation of all respiratory disease deaths.

Systems of ascertainment that are proposed include: 1) Identification of all hospitals in the community and the referral hospitals in the area; 2) development of a method for data acquisition based on current procedures by which hospital utilization is collected; 3) development of a system in each of the hospitals to identify all myocardial infarctions, coronary heart disease admissions and admissions for other atherosclerotic heart disease; 4) a death certficate review system to identify all arteriosclerotic heart disease, chronic heart disease, and cardiovascular disease deaths with a follow-back procedure including a review of hospital records, letters to physicians, medical examiner's and coroner's record and perhaps follow-back interviews to the next of kin.

Special sub-studies of the elderly in these communities might also be considered. Many of the previous studies suggested excess mortality related to airborne particles may be associated with cardiovascular disease among the elderly population. Thus, monitoring of the elderly population may be useful to determine the relationship between changes in inhaled particles, hospitalization and death among this susceptible sub-population.

The proposal envisioned is that a group of collaborating clinical centers would be selected of which one would serve as a data coordinating center. An

EPA group would also work closely with the clinical centers. The clinical centers, coordinating center and EPA staff would form a steering committee for the project. This committee would have the responsibility of monitoring the project as well as developing the specific protocols. Within the steering committee a special air monitoring group would be established, as well as a medical data group, which could then be sub-classified into pulmonary and cardiovascular measurement. Furthermore, a national advisory board should be established to review the activities of the steering committee periodically, and report to the EPA project officer on the status of the study. The steering committee will have the basic responsibility of writing the protocol, deciding on the sample sizes and based on funding, specific sub-projects within each of the areas. It is important to realize that the study should be of relatively long duration, and the centers that are selected become a major national resource for environmental problems. Thus, long-term funding for the study should be assured prior to its implementation.

A proposed time frame was then suggested. This included in year 1, the selection first, of the coordinating and data center and, secondarily, selection of the clinical centers based on the criteria previously presented. The selection of the geographical areas to be included in the study will require considerable amount of work for the EPA staff and perhaps outside consultants. Second, the coordinating center and collaborating clinical centers plus EPA staff would then spend a large part of the first year developing a specific protocol which would then be reviewed and approved by the national advisory committee. During this first year there would also be extensive training of the staff in the measurement of pulmonary function, the evaluation of cardiovascular diseases, and standardization of questionnaires. A critical point of the study is the comparability of data over time, both within staff members and among the different centers. During the first year there would also be pilot testing of a detailed air monitoring

system and the testing of the forms to be used in the clinical evaluation of pulmonary function measurement and the review of hospital records. Finally, at the end of the first year, there should be a refinement of the protocol based on the pilot evaluation and the final decisions on the selection of samples to be included in the specific studies. Samples that might be considered within each of the groups, as mentioned previously, would include pulmonary function studies, and symptoms and acute morbidity and mortality could be utilized. Studies of children would be useful especially prior to the age of cigarette smoking with more detailed studies of changes in pulmonary function in relationship to changes in inhalable particulates within and between communities. Certain high-risk groups could be followed, such as asthmatics, those with hyperactive airways, and, perhaps, individuals with chronic obstructive pulmonary disease identified both by pulmonary function and by clinical measurement. As noted, the design will include initial, detailed cross-sectional studies followed by yearly and bi-yearly pulmonary function and symptom surveys and continued long-term morbidity evaluation. More detailed pulmonary function studies could be done on specific sub-groups of the population based on the accuracy and reliability of the test and on the specific types of measurements that would be available. The decision as to the specific, more detailed pulmonary function studies would have to be left to the judgment of the steering committee, the advisory board and the availability of funds.

In order for this study to be successful, it was clearly agreed that very detailed and careful air monitoring must be done within all the communities. This needs to be standardized and carefully evaluated by the research investigators. The measurement techniques for pulmonary function, questionnaires, and morbidity studies must be carefully monitored and there must be a high degree of quality assurance within centers and between centers. There must be a long-term

commitment both of the Environmental Protection Agency and of the investigators within each of the communities to the study protocol.

The studies will be reasonably costly and turnover of staff, especially of senior investigators, could lead to a serious weakening of the study design. The populations should be selected carefully so that the levels of airborne particles can be related to the individuals' specific exposures. The population should be relatively stable so there will not be a substantial loss to follow-up, since this would have the potential of invalidating the results. Other pollutants within the community should be carefully evaluated. Communities where the levels of other pollutants are changing rapidly, or have a highly complex relationship with inhalable particles, should probably be avoided. Careful pilot testing of the program including both the air pollution monitoring and clinical evaluation should be done prior to embarking on a major study, and the national advisory committee which would carefully review the activities of the study protocol should be established.

Most of the committee members were relatively convinced that a variety of single isolated studies to look at the problem of inhalable particles, not clearly integrated, would have relatively little chance of success, and that a collaborative community study with standardized methods of measurement has the best potential for answering the problems that are being proposed.

In summary, the workshop members recommended that a prospective multicentered study relating airborne particles to cardiorespiratory morbidity and mortality be undertaken. The primary source of exposure could be coal-fired units or general urban air pollution, including photochemical oxidant. The members recommended that if possible the communities to be studied include those with high, medium, and low levels of pollution, with good historical data at least for total suspended

particles. High, intermediate, and low community mortality rates for cardiovascular disease could provide the basis for selecting communities for study, provided they met monitoring criteria. This design would result in a nine-community investigation, and coordination by a central data handling group would be essential.

Within this study design could also be incorporated special clinical or other studies of high-risk groups, such as juvenile asthmatics or elderly people with chronic respiratory disease. In any large-scale undertaking such as that proposed, careful standardization of methods is crucial, as is quality assurance both for air measurements, monitoring networks and clinical measurements. The recommendations of the panel concerning these aspects of the program have been detailed in the main body of the report.

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